

Risk Stratification and Early Oncologic Outcomes Following Robotic Prostatectomy

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ABSTRACT

Background and Objectives: Although the popularity of robotic-assisted laparoscopic prostatectomy is assured, little is known about the oncologic outcomes following the procedure.

Methods: We performed a retrospective cohort study including consecutive patients who underwent the surgery between 2003 and 2007 with at least 6 months of follow-up (n=464). Patients were stratified into low-, intermediate-, and high-risk groups according to D'Amico criteria. Biochemical failure was defined as a PSA ≥ 0.2 ng/mL.

Results: Of study patients, 256 (55%), 171 (37%), and 37 (8%) were classified as low-, intermediate-, and high-risk, respectively. Over a mean follow-up of 14.1 months (range, 6.0 to 55.3), 7.3% experienced biochemical failure. Biochemical disease-free survival at 30 months was 94%, 79%, and 73% among patients in the low-, intermediate-, and high-risk groups, respectively, ($P < 0.001$). Preoperative risk stratification was strongly associated with biochemical failure, with hazard ratios of 5.04 (95%: 1.52 to 16.7; $P < 0.001$) and 7.04 (95%: 1.39 to 35.6; $P < 0.001$) for intermediate- and high- over low-risk groups, respectively. The ability of risk stratification to predict biochemical failure had an area under the receiver operator characteristic curve of 0.74.

Conclusion: Robotic prostatectomy provides excellent cancer control outcomes for clinically localized disease.

Key Words: Prostatic neoplasms, Prostatectomy, Outcome assessment, Robotics.

INTRODUCTION

The American Cancer Society estimated that 186 320 new prostate cancer cases would be diagnosed in 2008, making it the most common form of cancer in men.¹ Because treatment of localized prostate cancer can be curative, accurate preoperative risk stratification is paramount in choosing optimal treatment. In 1998, D'Amico et al² retrospectively examined the outcomes of a large cohort of men with prostate cancer who underwent open radical prostatectomy, external beam radiation, and interstitial radiation with or without neoadjuvant androgen deprivation. The authors proposed a risk stratification scheme based on preoperative Gleason sum, prostatic-specific antigen (PSA), and clinical staging to predict biochemical failure. This risk stratification scheme has subsequently been externally validated following treatment with these same modalities.^{3,4} To our knowledge, no studies have compared the preoperative risk stratification with outcomes of men undergoing robot-assisted laparoscopic prostatectomy (RALP).

Since its introduction in the United States in 2000, RALP has become one of the most popular treatments for localized prostate cancer. Although numerous reports of perioperative and short-term functional outcomes exist,⁵⁻¹⁰ due to the novel nature of robotics and the indolent natural history of prostate cancer, there is a paucity of literature on oncologic outcomes.¹⁰⁻¹²

In this study, we report the early oncologic outcomes in patients who underwent RALP by a single surgeon over a recent 4-year period. Specifically, we assess the association between biochemical failure and perioperative variables, including D'Amico risk stratification in patients undergoing RALP with up to 55 months of follow-up.

METHODS

Study Population

We queried an IRB-approved database of 802 consecutive patients who underwent RALP by a single surgeon (DBS), between January 2003 and November 2007. Patients with insufficient clinical data to allow D'Amico risk stratifica-

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tion were excluded from the current analysis. Additionally, to ensure adequate oncologic follow-up, patients with less than 6 months of documented PSA data were also excluded, though all patients who failed biochemically prior to this time point were included.

Data Collection

Data collected in the database and assessed as part of the current analysis include age at surgery, body mass index (BMI, in kg/m^2), bladder neck involvement, margin status, prostate weight, postoperative Gleason score, number of nerve bundles spared, extra-capsular extension, capsular invasion, tumor multi-centricity, perineural invasion, presence of high-grade prostatic intraepithelial neoplasia (HG-PIN), seminal vesical involvement, and 1992 American Joint Commission of Cancer Staging (AJCC) clinical and pathologic cancer stage. BMI was calculated as weight in kilograms divided by height in meters squared. Based on clinical criteria, patients were stratified into risk categories as defined by D'Amico: low (PSA <10, Gleason <7, and AJCC stage cT2a or less); medium (PSA <20, Gleason <8, or AJCC stage cT2b); high (PSA \geq 20, Gleason >8, or AJCC cT2c or higher). Margin status was defined as any focal or multifocal involvement of tumor at the surgical margins on a pathological specimen. Postoperatively, PSA levels were determined at 6 weeks, and then again every 3 months for the first year, then every 6 months for the next 3 years, and then annually. The outcome for the current study was biochemical failure defined as the first occurrence of a postoperative PSA \geq 0.2 ng/mL.

Patient Care

In addition to a standard history and physical examination, all patients were evaluated preoperatively with PSA level and digital rectal examination. Slides of prostate needle biopsies were reviewed at our institution for confirmation of diagnosis and tumor grade. All patients with PSA levels >10 ng/mL underwent nuclear bone scan and computed tomography to evaluate for metastatic disease. Patients with cT2 disease or those with tumor involvement in all cores of a lateral side underwent endorectal MRI examination for evaluation of nerve involvement. Surgically appropriate patients with clinically localized disease were counseled regarding treatment options and offered surgical intervention. Robotic prostatectomy was performed by a single surgeon using a technique described elsewhere.¹³ No patient received either androgen deprivation therapy or radiotherapy without prior biochemical failure.

Statistical Analysis

Patient characteristics were calculated as means and prevalence for continuous and categorical variables, respectively, by biochemical failure status. The statistical significance of differences across biochemical failure status was determined using *t* tests for continuous variables and chi-square tests for categorical variables. Next, the longitudinal association between patient characteristics and biochemical failure was determined. For patients with biochemical failure, follow-up time was calculated as the number of months between their RALP and the first subsequent date when the patient had a PSA of \geq 0.2 ng/mL. For patients without a PSA \geq 0.2 ng/mL during follow-up (ie, those who remained free of biochemical failure), follow-up time was calculated as the number of months between RALP and their last PSA measurement. Biochemical disease-free survival was graphed according to D'Amico risk categories using the Kaplan-Meier method. The statistical significance of differences in biochemical disease-free survival across risk categories was determined using the log-rank test. Hazard ratios of biochemical failure were determined for patient characteristics via Cox proportional hazards regression models. Initially, unadjusted hazard ratios were calculated. Subsequently, multivariable hazard ratios were calculated by including postoperative Gleason score, extracapsular extension, positive margins, perineural invasion, and D'Amico risk category in an adjusted regression model. Due to collinearity with other variables, preoperative PSA and preoperative Gleason scores were not included in the multivariable adjusted model. Finally, we determined the area under the receiver operating characteristic (ROC) curve for how well risk categories at the time of RALP discriminate between patients who subsequently had and did not have a biochemical failure during follow-up. In an ROC curve, the true positive rate (sensitivity) is plotted as a function of the false-positive rate (100% - specificity) for different cut-off points of a test (ie, in this study, risk categories) providing a measure of the overall ability of a test to discriminate between cases of disease (ie, in this study, biochemical failure) and controls. Each point on a ROC curve represents a sensitivity/specificity pair corresponding to a particular risk category. In a test with the perfect ability to predict biochemical failure, the ROC curve will pass through the upper left corner (100% sensitivity, 100% specificity) of the plot. Therefore, the closer the ROC plot is to the upper left corner, the higher the overall accuracy of a test. A diagonal line on a plot (ie, the reference line from the bottom left to top right corner) represents a predictive test with the ability to detect out-

Table 1.
Characteristics of Patients by Failure Status

Patient Characteristics	Patients Without Failure (n = 430)	Patients With Failure (n = 34)	P-Value
Age*, years	59.2 (0.3)	60.4 (1.5)	0.46
Body mass index*, kg/m ²	27.0 (0.2)	26.8 (0.5)	0.71
Preop PSA			
<10	93%	74%	<0.01
10–19	6%	21%	
≥20	1%	6%	
Preop Gleason sum			
6	61%	24%	<0.01
7	33%	59%	
8	4%	9%	
9	2%	9%	
Preop clinical stage T1c	72.6%	79.4%	0.43
Pathologic weight†	46 (38 - 60)	41 (33 - 60)	0.26
Postop Gleason sum			
6	33%	6%	<0.01
7	60%	67%	
8	4%	12%	
9	3%	15%	
Nerve sparing‡	12%	23%	0.16
Extracapsular extension‡	15%	34%	0.01
Capsule invasion			
0	43%	34%	0.14
1	42%	38%	
2	14%	28%	
Multi-centricity	67%	63%	0.70
Margin positive	17%	39%	<0.01
Bladder neck invasion	2%	6%	0.21
Peri-neural invasion	63%	87%	<0.01
High grade PIN	87%	94%	0.41
D'Amico risk category			
Low	58%	15%	<0.01
Medium	35%	62%	
High	7%	24%	

*Mean (standard error).

†Median (25th to 75th percentiles).

‡Nerve sparing and extracapsular extension were dichotomized as yes or no.

comes consistent with random chance and an area under the curve value of 0.5. Values of the area under the curve >0.5 represent a test with discrimination better than chance. Statistical significance was defined as any $P < 0.05$. Analyses were performed using SAS (version 9.1, Cary, NC) and Stata (version 10.0, College Station, TX).

RESULTS

Between January 2003 and November 2007, 802 patients underwent RALP for clinically localized prostate cancer. After initially excluding 284 patients (35.4%) for insufficient PSA follow-up, an additional 54 (6.7%) were removed for lack of preoperative PSA documentation. The remaining 464 patients were included in the study. Of the 284 excluded patients, 219 had enough data for D'Amico risk stratification. In a separate analysis, the characteristics of these excluded patients were compared with those of the patients included in the analysis. There were no significant differences in age, preoperative PSA, pathological weight, D'Amico risk stratification, proportion of patients with extracapsular extension, HGPIN, perineural invasion, tumor multicentricity, margin status, Gleason score, pathological or clinical stage between patients included in and those excluded from the study (all $P > 0.20$); however, a significantly higher proportion of patients in the included analysis had bladder neck involvement over those who were excluded (2.7% vs. 0%, respectively, $P = 0.01$) (data not shown).

Of the 464 patients included in the study, mean/median (range) follow-up was 14.1/11.6 (range, 6.0 to 55.3) months. Overall, 256 (55%), 171 (37%), and 37 (8%) patients were categorized as having low-, medium-, and high-risk disease by D'Amico criteria, respectively. Thirty-four of 464 patients (7.3%) experienced biochemical failure at a mean/median (range) of 9.5/7.5 (range, 1 to 42.6) months following surgery.

Table 1 illustrates characteristics of patients for those who did and did not have biochemical failure during follow-up. Biopsy Gleason score, PSA, extracapsular extension, postoperative Gleason score, margin status, perineural invasion, and D'Amico risk classification were each associated with failure (all $P < 0.05$). Age, BMI, clinical stage, pathological weight, nerve sparing, capsular invasion, multicentricity, bladder neck invasion, and presence of HGPIN were not significantly associated with biochemical failure during follow-up. Actuarial BDFS at 30 months for patients in the low-, medium- and high-risk stratification categories were 94%, 79%, and 73%, respectively (**Figure 1**).

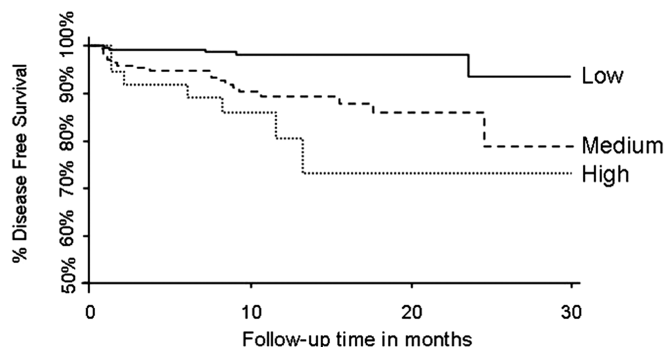


Figure 1. Kaplan-Meier curve showing risk of BDFS over time in low-, medium-, and high-risk patients. $P < 0.001$.

In a univariate time-to-event analysis, higher preoperative PSA, preoperative Gleason score, postoperative Gleason score, the presence of extracapsular extension, positive margins, peri-neural invasion, and medium and high D'Amico risk categories were associated with an increased hazard ratio of biochemical failure (**Table 2**). When controlling for these variables in multivariable analysis, D'Amico risk stratification was significantly associated with biochemical failure, with hazard ratios of 5.04 (95%: 1.52 to 16.7; $P < 0.001$) and 7.04 (95%: 1.39 to 35.6; $P < 0.001$) for medium- and high-risk categories compared with low-risk categories, respectively. No statistically significant difference was found between the outcomes of high-risk patients compared with those of intermediate risk; the hazard ratio was 1.65 (95%: 0.49 to 5.53; $P = 0.415$). Margin status, postoperative Gleason score, extracapsular extension, and perineural invasion were not associated with failure in the multivariate model.

The strength of D'Amico risk stratification in predicting biochemical failure is depicted in a receiver operator characteristic curve (**Figure 2**). The area under the curve for this variable was 0.74, suggesting reasonably good discriminatory power for predicting biochemical failure.

DISCUSSION

We report biochemical failure in 34 of 464 patients (7.3%) undergoing RALP with a mean (range) follow-up time of 14.1 (6 to 55.3). In our cohort, D'Amico risk stratification was associated with biochemical failure. Actuarial 30-month BDFS rates were 94%, 79%, and 73%, for low-, medium-, and high-risk patients, respectively. Our study supports the D'Amico risk stratification as an effective predictor of early outcomes following RALP. This is in accord with several recent external validations of the risk formula using large open radical prostatectomy cohorts.

Table 2.
Hazard Ratio of Failure Associated With Patient Characteristics

Characteristics	Unadjusted	Multivariate-Adjusted§
Preop PSA		
<10	1.00 (ref)	-
10–19	4.36 (1.88–10.1)*	-
≥20	8.38 (1.96–35.8)*	-
Preop Gleason sum		
6	1.00 (ref)	-
7	3.99 (1.75–9.07)†	-
8	3.93 (1.03–15.0)‡	-
9	8.99 (2.37–34.1)†	-
Postop Gleason sum		
5 or 6	1.00 (ref)	1.00 (ref)
7	5.57 (1.31–23.7)‡	1.38 (0.26–7.34)
8	11.3 (2.07–62.4)†	1.98 (0.27–14.7)
9	19.3 (3.73–99.7)*	1.62 (0.18–14.6)
Extracapsular extension	2.46 (1.18–5.13)‡	1.13 (0.51–2.47)
Margin positive	2.73 (1.35–5.54)†	1.87 (0.84–4.14)
Perineural invasion	3.72 (1.30–10.7)‡	1.71 (0.55–5.36)
D'Amico risk category		
Low	1.00 (ref)	1.00 (ref)
Medium	6.07 (2.29–16.1)*	5.04 (1.52–16.7)†
High	10.4 (3.37–31.8)*	7.04 (1.39–35.6)‡

*P<0.001.

†P<0.01.

‡P<0.05.

§Variables not included in regression model for characteristics without data presented (-). Multivariate model includes all variables in the same regression model.

The Mayo Clinic³ reported 5-year BDFS rates of 90%, 78%, and 68% from 7591 low-, medium-, and high-risk patients, respectively. Another group from Johns Hopkins⁴ published their data on 6652 men, showing 5-year BDFS rates of 94.5%, 76.6%, and 54.6%, in the 3 respective risk groups. The University of California San Francisco group¹⁴ documented 78%, 63%, and 60% 5-year BDFS rates in their cohort of 1701 men registered in the CapSURE database. In this latter study, while low-risk BDFS was significantly better than those of intermediate- and higher-risk patients, the group noted no significant difference in outcomes between the latter 2 groups. We report a similar statistically insignificant trend towards worse BDFS in high-risk over intermediate-risk patients; however, with only 8% of

our cohort having high-risk disease, we are limited in supporting any conclusions regarding the predictive ability of intermediate- versus high-risk classification. We can, however, conclude that in accordance with the above-mentioned reports, our study also found D'Amico risk stratification to be predictive of biochemical recurrence. Although our cohort is substantially smaller than the mentioned studies, and our follow-up is significantly shorter, to our knowledge, our study is the first to evaluate the significance of risk stratification on early outcomes in a robotic cohort.

While no RALP series has yet reported oncologic outcomes using the D'Amico risk stratification, a few studies

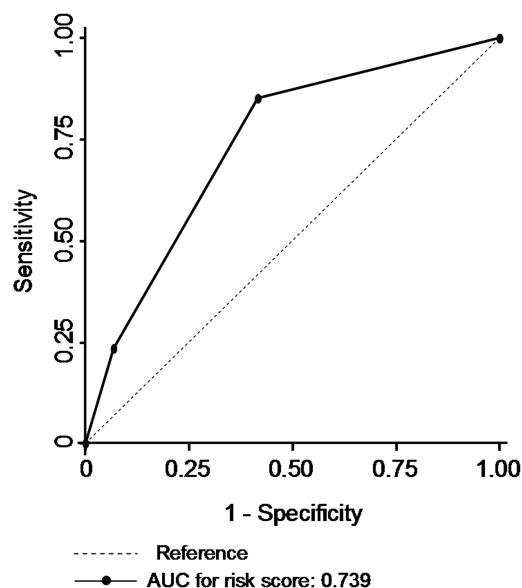


Figure 2. Receiver operator characteristic curve showing the strength of D'Amico risk stratification in predicting biochemical failure.

have reported overall oncologic outcomes following RALP. In the largest series to date, the Henry Ford group¹² reports outcomes of 2766 patients. At a median (range) follow-up time of 22 months (range, 7 to 71), the group reports a 7.3% PSA recurrence rate, coincidentally identical to our overall recurrence rate. The Cornell group reports¹¹ 4 failures in 132 men (3%) after 1 year of follow-up. Patel and colleagues¹⁰ reported their experience with their initial 200 cases and report a PSA recurrence rate of 5% at an average follow-up time of 9.7 months. Although the authors do not comment on risk stratification specifically, they note that neither patients with pT2 disease nor those with pT3a disease and focally extracapsular extension experienced recurrence during their brief follow-up. The University of Chicago group¹⁵ also reported their experiences and noted an overall biochemical recurrence rate of 4.8% in 945 patients after a median follow-up of 15.6 months. The paper reports specifically on the significance of BMI on outcomes; in accordance with our results, the authors report no association between recurrence and BMI.

The greatest limitation in our study is the follow-up time, which was only 14.1 months. Although prior studies have shown disease progression can occur up to 15 years following diagnosis of untreated disease, over 90% of biochemical recurrences following radical prostatectomy are reported to occur within the first 5 years following surgery.^{16,17} In addition, it is acknowledged that BDFS is a

surrogate, but not a substitute for the more clinically relevant outcome of overall disease-specific survival. As the field of robotic prostate surgery matures, 5-year outcomes of large cohorts are imminent; however, until then, these early outcomes offer useful information to consider when counseling patients and deciding on treatment.

In our study, although margin status was associated with outcome in a univariate analysis, a multivariate regression model shows no significant association between margins and biochemical failure. However, this may be an artifact of the statistics, as margin positivity may be associated with risk category. Thus, we can not discount the role of significance of margins on biochemical failure in our cohort. Overall, we experienced an 18.8% positive margin rate, including patients of all pathologic stages. The overall rate of margin positivity in published RALP studies is variable (range, 2% to 59%), depending on surgeon experience, cohort size, and distribution of pathologic stages.¹⁸ Contemporary large series from experienced surgeons report positive margin rates ranging from 10.5% to 17.3%.^{10,12,19–22} The significance of positive margins is unclear. In the open prostatectomy literature, studies can be found supporting or refuting the association between positive margins and oncologic outcomes. While margin location and extent of margin involvement are beyond the scope of this article, studies have also suggested these variables to also be associated with risk profile and biochemical failure.^{22,23} As more outcomes are published, it would be of great interest to further examine the significance of such findings in patients undergoing RALP.

CONCLUSION

We report a 7.3% rate of biochemical failure at a mean of 14.1 months of follow-up after RALP in 464 patients. Our early oncologic outcomes were significantly associated with D'Amico risk stratification and clinical stage and appear to be similar to oncologic outcomes of larger radical prostatectomy series.

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